Pharmacokinetic Interactions Between the HCV NS5A Inhibitor MK-8742 and Tenofovir (TDF), Raltegravir (RAL), and Efavirenz (EFV)


Background: MK-8742, an inhibitor of the hepatitis C virus (HCV) NS5A protein, is being developed for the treatment of chronic hepatitis C. HCV infections are a major cause of mortality, and oral drugs are preferred over parenterally administered peginterferon/ribavirin (PR) regimens.

Objectives: To investigate pharmacokinetic (PK) interactions between MK-8742 and either TDF, RAL, or EFV in part 1, and to determine the safety and tolerability of the MK-8742 + RAL + EFV combination regimen in part 2.

Study Design: Part 1 included 3 periods, with 10 subjects per period: period 1, MK-8742 alone (50 mg once daily for 8 days); period 2, MK-8742 alone (50 mg once daily), then washout for ≥7 days; period 3, MK-8742 (50 mg once daily) + RAL (single dose 400 mg) + EFV (single dose 50 mg), then washout for ≥7 days. In part 2, 10 subjects received MK-8742 (50 mg once daily) for 8 days, then washout for ≥7 days, followed by MK-8742 (50 mg once daily) + EFV (600 mg once daily) for 8 days.

Results: MK-8742 concentrations decreased following coadministration with EFV, possibly as a result of CYP3A4 inhibition. The most commonly reported AEs were headache (n = 4), diarrhea (n = 3), and abdominal pain (n = 2).

Conclusions: Coadministration of MK-8742 with EFV did not meaningfully alter the C\textsubscript{\text{EFV:predose}}, and up to 24 hours postdose in periods 2 and 3 in part 3. The most commonly reported AEs were drug eruption, dizziness, and feeling intoxicated (n = 3 each, all in subjects coadministered with a single dose of MK-8742).

Safety and Tolerability: No clinically significant adverse events were reported.

Summary and Conclusions: MK-8742 concentrations decreased following coadministration with EFV, possibly as a result of CYP3A4 inhibition. The most commonly reported AEs were headache, diarrhea, and abdominal pain. No clinically significant adverse events were reported.

Disclosures: This study was funded by Merck & Co., Inc., Whitehouse Station, NJ.
Pharmacokinetic Interactions Between the HCV NS5A Inhibitor MK-8742 and Tenofovir (TDF), Raltegravir (RAL), and Efavirenz (EFV)

W W. Yeh, W. Marshall, J. Ma, E. Mangan, X. Huang, Y. Zhu, S. Langley, P. Jumes, G. Youngberg, and J. B. Rutterton

1Merck Sharp & Dohme Corp., Whitehouse Station, NJ USA; 2Celeron, Lincoln, NE, USA

Abstract

Background: MK-8742, an inhibitor of the hepatitis C virus (HCV) NS5A protein, is being developed for the treatment of HCV infection. HCV interferes with host metabolism, and studies in patients coinfected with human immunodeficiency virus (HIV) suggest that concomitant administration of HIV drugs could alter the pharmacokinetics of MK-8742. In the current study, we examined the pharmacokinetic interactions of MK-8742 with a single dose of Raltegravir (RAL) or Efavirenz (EFV), drugs known to interact with the cytochrome P450 (CYP) enzyme system.

Methods: Concomitant administration of MK-8742 with either RAL or EFV did not meaningfully alter the CYP3A4 or CYP2B6 enzyme system. MK-8742 concentrations decreased following coadministration with EFV, possibly as a result of CYP3A4 induction by EFV.

Results:

Concomitant administration of MK-8742 with RAL did not meaningfully alter the CYP3A4 or CYP2B6 enzyme system. MK-8742 concentrations decreased following coadministration with EFV, possibly as a result of CYP3A4 induction by EFV.

Conclusion: MK-8742 can be coadministered with RAL or EFV without altering the steady-state AUC of MK-8742.

Keywords: MK-8742, Ombitasvir, HIV, HCV, CYP3A4, CYP2B6, Raltegravir, Efavirenz

Safety and Tolerability

No deaths or serious AEs were reported. There were also no consistent treatment-related changes in laboratory values, vital signs, or ECGs. A single dose of MK-8742 in the presence of EFV did not meaningfully alter the plasma AUC of MK-8742.

Conclusion: MK-8742 can be coadministered with RAL or EFV without altering the steady-state AUC of MK-8742.

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WW Yeh, W Marshall, J Ma, E Mangel, X Huang, Y Zhu, S Langley, P Jumes, Y Youngberg, JR Butterton

1Merck Sharp & Dohme Corp., Whitehouse Station, NJ, USA; 2Celerion, Lincoln, NE, USA

Abstract

Background: MK-8742 is an inhibitor of the Hepatitis C Virus (HCV) NS5A. By blocking the activity of NS5A, MK-8742 can impede viral replication and, thus, reduce the production of new viral particles. This study evaluated the pharmacokinetic interactions and safety of MK-8742 coadministered with either TDF, RAL, or EFV in healthy subjects.

Methods: In all 3 parts of the study, most patients were white and non-Hispanic/non-Latino. BMI = body mass index; EFV = efavirenz; RAL = raltegravir; TDF = tenofovir.

Results

Patient Demographics

<table>
<thead>
<tr>
<th>Ethnicity</th>
<th>n</th>
<th>Gender</th>
<th>Male:Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>White</td>
<td>9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>1</td>
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</table>

PK Parameters

<table>
<thead>
<tr>
<th>Pharmacokinetic Parameter</th>
<th>MK-8742 Alone</th>
<th>MK-8742 + TDF</th>
<th>MK-8742 + RAL</th>
<th>MK-8742 + EFV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax (µg/mL)</td>
<td>3.04, 3.58</td>
<td>8.56, 9.09</td>
<td>4.46, 4.98</td>
<td>2.28, 2.74</td>
</tr>
<tr>
<td>AUC0-24 (µg·h/mL)</td>
<td>31.29, 41.47</td>
<td>57.54, 68.19</td>
<td>247.13, 301.17</td>
<td>183.27, 224.92</td>
</tr>
<tr>
<td>T1/2 (h)</td>
<td>5.07 (2.94–12.57)</td>
<td>8.14 (5.41–11.15)</td>
<td>5.77 (4.16–8.04)</td>
<td>9.03 (6.45–12.37)</td>
</tr>
</tbody>
</table>

Conclusion: Coadministration of MK-8742 with TDF did not result in clinically meaningful drug-drug interactions. MK-8742 concentrations decreased following coadministration with EFV, possibly as a result of CYP3A4 inhibition by EFV. One subject reported 2 AEs of fatigue both of which were considered to be related to MK-8742 (MK-8742 alone, n = 1; MK-8742 + RAL, n = 1).

Summary and Conclusions

MK-8742 pharmacokinetics were not altered by concomitant treatment with TDF, RAL, or EFV. MK-8742 + TDF did not result in clinically meaningful drug-drug interactions. MK-8742 concentrations decreased following coadministration with EFV, possibly as a result of CYP3A4 inhibition by EFV. One subject reported 2 AEs of fatigue both of which were considered to be related to MK-8742 (MK-8742 alone, n = 1; MK-8742 + RAL, n = 1).

Disclosures

SY had a financial relationship within the last 12 months relevant to this presentation with Merck & Co., Inc., Whitehouse Station, NJ.

This research was funded by Merck & Co., Inc., Whitehouse Station, NJ.

References


4. EFV Pharmacokinetics

<table>
<thead>
<tr>
<th>Pharmacokinetic Parameter</th>
<th>MK-8742 Alone</th>
<th>MK-8742 + TDF</th>
<th>MK-8742 + RAL</th>
<th>MK-8742 + EFV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax (µg/mL)</td>
<td>2.50, 3.10</td>
<td>5.00, 6.20</td>
<td>3.00, 3.70</td>
<td>1.50, 2.00</td>
</tr>
<tr>
<td>AUC0-24 (µg·h/mL)</td>
<td>18.75, 22.65</td>
<td>37.50, 45.30</td>
<td>28.75, 34.65</td>
<td>15.75, 19.60</td>
</tr>
<tr>
<td>T1/2 (h)</td>
<td>4.60 (3.00–7.20)</td>
<td>8.80 (5.40–12.30)</td>
<td>6.00 (4.20–8.40)</td>
<td>10.00 (7.20–12.80)</td>
</tr>
</tbody>
</table>

EFV Pharmacokinetics

<table>
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<tr>
<th>Pharmacokinetic Parameter</th>
<th>MK-8742 Alone</th>
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<th>MK-8742 + EFV</th>
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<tbody>
<tr>
<td>Cmax (µg/mL)</td>
<td>2.00, 2.50</td>
<td>4.00, 5.00</td>
<td>3.00, 3.50</td>
<td>1.50, 2.00</td>
</tr>
<tr>
<td>AUC0-24 (µg·h/mL)</td>
<td>10.00, 12.50</td>
<td>20.00, 25.00</td>
<td>15.00, 18.75</td>
<td>7.50, 10.00</td>
</tr>
<tr>
<td>T1/2 (h)</td>
<td>3.00 (2.00–4.50)</td>
<td>6.00 (4.00–8.00)</td>
<td>4.50 (3.00–6.00)</td>
<td>7.50 (5.00–10.00)</td>
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EFV Pharmacokinetics

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<td>3.00, 4.00</td>
<td>2.50, 3.00</td>
<td>1.00, 1.50</td>
</tr>
<tr>
<td>AUC0-24 (µg·h/mL)</td>
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<td>15.00, 20.00</td>
<td>12.50, 15.00</td>
<td>5.00, 7.50</td>
</tr>
<tr>
<td>T1/2 (h)</td>
<td>2.50 (1.50–3.50)</td>
<td>5.00 (3.50–7.00)</td>
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WW Yan, W Marshall, J Ma, E Meng, L Xuangang, Y Zhu, S Langleby, P James, Y Youngberg, JR Butterton

1Merck Sharp & Dohme Corp., Whitehouse Station, NJ, USA; 2Celerion, Lincoln, NE, USA

Abstract

Background: MK-8742, an investigational compound, is being developed as a once-daily treatment for chronic hepatitis C (HCV) infection. MK-8742 is a potent inhibitor of the hepatitis C virus (HCV) NS5A, a target for antiviral therapy. This study was designed to evaluate the pharmacokinetic interactions between MK-8742, TDF, and EFV in healthy subjects and patients with HCV/HIV coinfection undergoing therapy with MK-8742.

Methods: This study consisted of 3 parts, each part comparing MK-8742 alone and MK-8742 coadministered with a single oral dose of TDF or EFV coadministered once daily for 8 days. Safety assessments included continuous monitoring of clinical laboratory tests, vital signs, and ECGs. Serum samples were collected predose and during up to 24 hours postdose in periods 2 and 3 in part 3.

Results: The most commonly reported AEs were headache (n = 4), diarrhea (n = 3), and abdominal pain (n = 2). There were no deaths or serious AEs reported. There were also no consistent treatment-related changes in laboratory values.

Conclusion: MK-8742 is well tolerated in combination with TDF and EFV in healthy subjects and patients with HCV/HIV coinfection undergoing therapy with MK-8742.

Keywords: MK-8742, TDF, EFV, HCV, HIV, pharmacokinetics, safety, tolerability

Patients and Methods

Subjects

60 healthy adult male volunteers, aged 18–50 years, were selected in each part to evaluate the safety and tolerability of MK-8742 alone and MK-8742 coadministered with TDF or EFV. All subjects were non-smokers and were not pregnant or planning to become pregnant during the study.

Design

This study consisted of 3 parts, each part comparing MK-8742 alone and MK-8742 coadministered with a single oral dose of TDF or EFV coadministered once daily for 8 days. Safety assessments included continuous monitoring of clinical laboratory tests, vital signs, and ECGs. Serum samples were collected predose and during up to 24 hours postdose in periods 2 and 3 in part 3.

Pharmacokinetics

MK-8742 Alone

MK-8742 Coadministered with TDF

MK-8742 Coadministered with EFV

Conclusion: MK-8742 is well tolerated in combination with TDF and EFV in healthy subjects and patients with HCV/HIV coinfection undergoing therapy with MK-8742.

Keywords: MK-8742, TDF, EFV, HCV, HIV, pharmacokinetics, safety, tolerability

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Safety and Tolerability

MK-8742 Alone

MK-8742 Coadministered with TDF

MK-8742 Coadministered with EFV

Summary and Conclusions

MK-8742 is well tolerated in combination with TDF and EFV in healthy subjects and patients with HCV/HIV coinfection undergoing therapy with MK-8742.

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